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MEETING MODERN DATA INTEGRITY AND COMPLIANCE REGULATIONS

FDA was perhaps understating a point when it said in its April 2016 Draft Guidance: *Data Integrity and Compliance with cGMP*[1] that the increasing number of data integrity-related cGMP violations identified during its inspections was 'troubling'. In fact, 21 out of 28 warning letters issued by the agency between January 2015 and May 2016 involved data integrity issues in drug manufacturing[2].

Ultimately, whether you are a drug manufacturer, clinical research organization (CRO) or pharmaceutical R&D company, FDA compliance as well as the accuracy and completeness of data is critical for safe product development, and any breach of data integrity could have serious implications for human health.

cGMP violations identified through routine regulatory inspections are manifold. Regulators do witness some intentional violations, perhaps the destruction of paper records, or the failure to take corrective action to address open investigations into interrupted, missing, deleted or lost data. However, in most cases non-compliance is not the result of overt misconduct, but stems from inadequate or poorly implemented procedures, ineffectual computer system security – think shared logins and permissions – and poor understanding of and adherence to internal practices, SOPs and controls, and what data integrity is.

The Very Real Costs of Non-Compliance

- The costs of non-compliance for one global manufacturer that in 2015 received an FDA warning letter and important ban relating to two facilities, was estimated to be between $148 million and $178 million. The company's exports dropped by $48 million, and costs associated with remediation and write-down were expected to be somewhere between $40 million and $70 million. An estimated 41 ANDAs and 38 DMFs were at risk of delay[3].
- Between 2013 and 2015 another manufacturer received FDA import alerts relating to two of its facilities, MHRA recall of multiple products and finally the recall of all U.S. products. Associated costs were projected to reach $911 million, including revenue losses of $760 million. The firm also lost $2.3 billion in its market capitalization[3].
- A warning letter received by one manufacturer in 2015[3] led to a previously FDA-approved innovator drug being rescinded, and the relocation of generic production. Total costs were estimated to be in the region of $113-133 million, with remediation costs and write-downs projected to be in the region of $25-45 million[3].

In a quality control setting, laboratory staff who are under pressure to reduce delays might opt to repeat sample retesting until they get desired results, or fail to report or investigate out of specification (OOS) or anomalous test results. Sometimes violations of good practice and non-adherence to healthcare compliance regulations, whether in a clinical or manufacturing environment, may simply be due to the continued use of outdated or unqualified electronic systems.

FDA's Q&A style draft guidance serves as a starting point for FDA compliance to give the manufacturing sector a push in the right direction to avoiding compliance regulation issues and ensuring data integrity. Accordingly, it is important that companies properly assess what is data integrity in healthcare. For instance, one key sentence in the draft guidance sums up what companies should remember. It states: "When generated to satisfy a cGMP requirement, all data become a cGMP record." In other words, every piece of data counts. Drug manufacturers must take this basic tenet on board if they are to meet cGMP fully. But equally, this same principle also applies to the CROs and the need to meet Good Clinical Practice (GCP) requirements.

Regulators including FDA, the European Commission's European Medicines Agency (EMA) and the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) take a 'guilty until proven innocent' stance when there is any evidence of non-compliance. The regulator will determine the scope of the problem, but it is up to the at fault organization to take satisfactory remedial action.

For manufacturers the repercussions may include production stoppages, distribution and import bans, regulatory approval delays, and product recalls. Manufacturers and CROs who are found to be in violation of cGMP and/or FDA compliance may also lose the trust and good will of the regulators, and could face increased scrutiny through more frequent and in depth inspections. Personal and corporate prosecutions are also becoming more common.

In May 2017, for example, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended against approving one French pharmaceutical company's orphan disease drug[4], for reasons including limited data on the safety of the medicine, and the findings of a routine GCP inspection at clinical trial sites, which revealed what the CHMP termed "serious failings in the way the study had been conducted."

Outside of the regulatory repercussions, companies' reputations, share prices and profits also suffer. CROs and CDMOs lose clients and product- or service-related profits. Remediation costs can be substantial, and brands and confidence in industry are damaged. In a worst case scenario patients with diseases for which there are limited treatment options could feasibly be faced with a life-saving medicines shortage, if the supply chain is broken. Back in 2009, for example, a U.S. biotech company had to temporarily shut down production at one of its biomanufacturing plants[5] due to viral contamination in one of its bioreactors. This resulted in serious shortages of two drugs for orphan diseases.

Data Integrity Criteria

The ALCOA acronym is commonly used to summarize criteria for ensuring data integrity, whether that data is based on acceptable paper, or electronic records.

Attributable: Who performed the action and when? If a record is changed, who changed it and why? Is there a link to the source data? Have user credentials and permissions been checked.

Legible: Data must be recorded permanently in a durable medium and be readable and understandable. Have recorded data and results been checked before being recorded?

Contemporaneous: The data should be recorded at the time the work is performed and date and time stamps should follow in order.

Original: The information must include the original record or a certified true copy of the original, including all metadata.

Accurate: There should be no errors, or editing performed without documentation of amendments. Data should also be verified as correct.

So what strategies should companies put in place to make sure they are in cGMP and FDA compliance with regulatory requirements and keep data integrity a priority? Ongoing training is a must, along with promoting an enterprise-wide philosophy that encourages the establishment of risk-based strategies and policies to meet cGMP, or GCP imperatives from the ground up.

Data Integrity is Everyone's Responsibility

Make it the business of everyone in the company to understand the importance of maintaining data integrity and highlight potential failings in procedures, data management and security. It's then less likely that inadequate processes will go un-noticed, or that staff will cut corners. This approach will ultimately be less costly than having to implement remediation.

An Infrastructure to Support Laboratory Compliance Throughout the Product Lifecycle

STARLIMS has developed its STARLIMS laboratory informatics management system (LIMS) as a configurable, enterprise-wide cGMP, GCP, and FDA compliance-featured data management infrastructure that underpins all laboratory data collection, management and reporting across R&D, clinical and manufacturing sectors. Designed to handle complex workflows and processes, the platform ensures that validated protocols for processes and data acquisition and management are followed for all procedures in manufacturing, quality control and clinical research laboratories.

STARLIMS is designed to support ALCOA obligations and facilitate process standardization. The platform interfaces with enterprise systems and integrates with analytical and measurement instrumentation to automate data collection,

archiving and reporting, and minimize the possibility of unintentional transcription errors or loss of data from paper-based recording.

Adopt Electronic Signatures

Adopting CFR Part 11 compliant electronic signatures instead of handwritten signatures is not only more efficient but also prevents the possibility of backdating records. Electronic signatures also result in a more complete audit trail than manual signatures.

STARLIMS allows users to configure which individual actions require an electronic signature, password, comment and witness or any combination of these elements. This means that critical healthcare compliance regulations and tasks are fully documented.

Enforce Strong Password Policies

Best practices in password management set some standards to prevent an attack on the system and to prevent unauthorized manipulation of data. By creating, enforcing and documenting strong password policies, an organization is creating the first line of defense in the protection of data integrity.

STARLIMS User Management supports best practices in password management such as content and length definition, failed attempts lockout, password expiration and reuse restrictions.

Delineate User Roles

The FDA suggests that the System Administrator role, including any rights to alter files and settings, "be assigned to personnel independent from those responsible for the record content." In addition, there are many workflow scenarios where it is essential from a data integrity perspective to ensure that result reviews for release are completed by a person other than the individual who entered the data. By clearly defining and assigning user roles, each user can have a tailored workflow that maintains healthcare compliance regulations without manual intervention.

STARLIMS allows unlimited User Role definition and gives complete control of task management by role, user, organization, site or any combination of these parameters.

Create Data Manipulation SOP

A significant number of FDA citations involve inadequate documentation relating to the handling of raw data from instrumentation, laboratory notebook data or other data used prior to final reporting. The creation of an SOP to address these situations provides guidelines that assist analysts in exercising good judgment when manipulating raw data, and provides a method for documenting any changes that are made.

STARLIMS provides access to the laboratory's SOPs directly from the corresponding workflow so the analyst has the information they need at the time they need it, without having to search through manual binders or, even worse, not referring to SOPs at all because they are not conveniently available.

Train, Train and Retrain!

Creating safeguards and establishing preventive measures and support for data integrity will only be effective if they are known and understood by the laboratory staff (e.g., asking questions such as what is data integrity?). Training is one task that is often overlooked and FDA inspectors will frequently uncover this deficiency during their inspections. An effective training program will not only close the gap but will also reinforce policies and procedures on an ongoing basis.

STARLIMS provides online tools to schedule employee training programs and monitor completion by employees. Individual certification records can in addition be tied to specific test workflows for each employee, which strengthens the laboratory's commitment to data integrity, quality and FDA compliance.

Self-Inspect Regularly

The results of an FDA inspection should not be a surprise. Conducting regular mock inspections will allow management to identify areas for improvement before the next inspection. The time and effort invested in a self-inspection is a fraction of that which may be required as part of remediation following an FDA warning.

STARLIMS provides full traceability and audit trail records from an individual test level to an overall site or organization level. In addition, data integrity can be monitored in real-time via role-specific analytical dashboards, which can also be used as investigational tools, as needed.

STARLIMS makes it easier for laboratories to adopt and adhere to best practices and procedures, to help ensure that they meet cGMP and GCP compliance regulations. By offering a regulatory compliance-featured framework that promotes proactivity, and helps to prevent common compliance pitfalls and unexpected deficits at regulatory inspection, STARLIMS supports a practical approach to ensuring data integrity, security, and enterprise-wide operational excellence.

[1] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm495891.pdf

[2] https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm518522.pdf

[3] The Real Cost of Poor Data Integrity in Pharmaceutical Manufacturing. Lachman Consultant Services, Inc.

[4] http://www.ab-science.com/file_bdd/content/1495041283_CPMCO_vENVF.pdf

[5] http://news.genzyme.com/press-release/genzyme-temporarily-interrupts-production-allston-plant

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